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For and on behalf of RWS Group Ltd

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File Reference A 584/2003

The Austrian Patent Office herewith certifies that

BIOCHEMIE GmbH
of A-6250 Kundl/Tyrol
(Tyrol),

filed a patent application on the **16 April 2003**
relating to

“Organic compounds”,

and that the attached description entirely agrees with the original description filed
simultaneously with this Patent Application.

Austrian Patent Office
Vienna, 11 March 2004

The President
pp
[Stamp of the Austrian Patent Office]
[signature]

HRNCIR
Senior Technical Inspector

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A 584/2003

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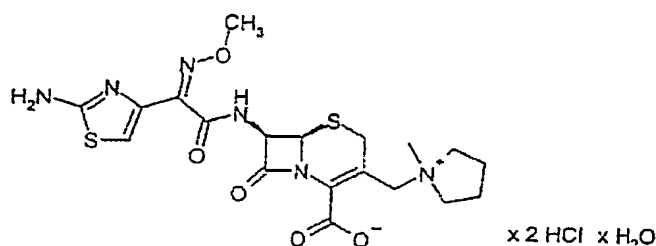
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Organic compounds

The present invention relates to the preparation of
 1-[[[(6R,7R)-7-[[[(2Z)-(2-amino-4-thiazolyl)methoxy-
 imino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-
 azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrol-
 idinium dihydrochloride hydrate (cefepime
 dihydrochloride



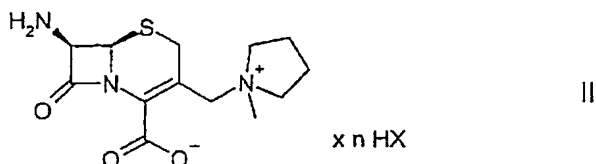
monohydrate). Cefepime is a valuable 4th generation
 injectable cephalosporin with antibacterial properties,
 see e.g. The Merck Index Thirteenth Edition, Item 1935.

The preparation of cefepime is not simple. For example,
 it is known that the 7-acyl side chain as the
 difficult-to-obtain 2-(2-aminothiazol-4-yl)-2-methoxy-
 imino-acetic acid chloride hydrochloride must be used
 for the production of cefepime, in order to obtain an
 active ingredient which is pure in respect of the by-
 products anti-isomer and Δ -2 isomer.

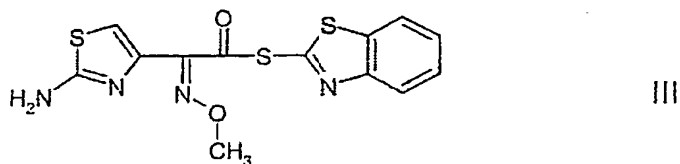
A novel process for the production of cefepime has been
 found which is notable for the simplicity of the choice
 of solvent and the accessibility and easy handling of
 the 7-acyl side chain, and which at the same time leads
 to an active ingredient with high purity in respect of
 the abovementioned by-products.

The process comprises the reaction of a pyrrolidinium-
 1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]-

oct-2-en-yl)methyl]-halide, an acid addition salt thereof or its free base of formula II



wherein n is 0-2 and X is chloride, bromide or iodide
5 with (Z)-(2-aminothiazol-4-yl)methoxyimino-acetic acid-
2-mercaptobenzothiazolyylester of formula III



in an acetonic or aqueous/acetonic solution, optionally
in the presence of a base, wherein cefepime
10 dihydrochloride monohydrate is isolated directly from
the reaction mixture by adding HCl.

The process is extremely simple.

15 Neither extraction steps nor more complex purification
operations are necessary.

The solvent regeneration is an especially simple
procedure, in that only one solvent is used both for
20 the acylation reaction and for the crystallisation
step.

The intermediate compound of formula II may be present as mono-addition salt or di-addition salt. In addition, the intermediate of formula II may be present in the form of a solvate, for example a hydrate. The usual
5 addition-salts are represented by the mono- and dihydrochloride or the hydriodide.

Depending on the salt form, the corresponding acid addition salt is released for the reaction with the
10 acylation agent with the assistance of the necessary amount of a base, preferably a trialkylamine. Accordingly, a mono-addition salt is released with approximately one molar equivalent of base, and a di-addition salt is correspondingly released with
15 approximately two. However, it is also possible to react the corresponding acid addition salt with (Z)-(2-aminothiazol-4-yl)methoxyimino-acetic acid-2-mercapto-benzothiazoly-lester without adding a base.

20 If the intermediate of formula II is used as the mono- or dihydrochloride, the active ingredient cefepime is naturally obtained as the pure dihydrochloride. If the intermediate is used as the hydriodide, the recrystallised product is practically free from traces
25 of iodide.

Alternatively, foreign ions can be removed from the reaction solutions by methods known per se, for example with the assistance of an anion exchanger.

30

Suitable trialkylamines are C₁-C₈-trialkylamines, for example triethylamine or tributylamine. The presence of water in the acylation reaction in principle also allows the use of inorganic bases, for example sodium
35 or potassium hydroxide or an alkali hydrogen carbonate or alkali carbonate.

The reaction is preferably carried out in the presence of water: the amount of water is not critical; there must be balanced solubility of the cephalosporin intermediate of formula II on the one hand and of the active ester of formula III on the other hand. The water/acetone ratio is about 1:10 to 10:1, and preferably a water/acetone ratio of 1:1 to 1:5 is used for the acylation reaction. After the acylation reaction, in order to crystallise cefepime dihydrochloride, hydrochloric acid is added, preferably aqueous concentrated hydrochloric acid, and a pH value of less than 3, preferably less than 1, is set. By adding acetone, the crystallisation of cefepime dihydrochloride is then completed. Preferred water/acetone ratios in the crystallisation step are ratios of 1:1 to 1:20, especially ratios of 1:3 to 1:10.

The examples below elucidate the invention in more detail.

Example 1

Preparation of 1-[[[(6R,7R)-7-[[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-1-pyrrolidinium dihydrochloride hydrate

44.3 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate (NMP-ACA) are suspended in a mixture of 200 ml of H₂O and 400 ml of acetone. 38.5 g of (Z)-(2-aminothiazol-4-yl)methoxy-iminoacetic acid-2-mercapto-benzothiazolylester are added to the suspension. At a temperature of ca. 15°C, a mixture of 13.9 ml of triethylamine and 14 ml of acetone is slowly added dropwise to the suspension over the course of 3 hours.

The resulting cloudy solution is stirred for a total of 6.5 hours at 20°C.

33 ml of 37% HCl are subsequently added to the reaction mixture, and then ca. 300 ml of acetone are added whilst stirring. The mixture is seeded with seed crystals, and within ca. 90 minutes a suspension is produced. Subsequently, within 90 minutes, 1700 ml of acetone are added dropwise whilst stirring gently. The suspension is stirred for a further one hour at room temperature, and then the title compound is isolated through a suction filter, and the product is washed with 250 ml of acetone/H₂O mixture (90/10) and with a total of 500 ml of acetone in two portions. The product is subsequently dried for ca. 18 hours at room temperature in a vacuum drying chamber.

Yield 51.8 g

purity: HPLC: 98.8 area percent

20 Example 2

Recrystallisation of 1-[[[(6R,7R)-7-[[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium dihydrochloride hydrate

25 50.0 g of cefepime dihydrochloride hydrate are dissolved in 200 ml of H₂O. 22 ml of 6 n HCl are added and then the solution is mixed with 5 g of activated carbon. The suspension is stirred for 10 minutes at room temperature and then filtered through a suction filter. The filter layer is then washed with 50 ml of H₂O, and the combined filtrates are mixed with 600 ml of acetone until turbidity occurs. The resulting suspension is stirred for 15 minutes and then a further 30 1400 ml of acetone are added over the course of one hour whilst stirring gently. The suspension is stirred for another one hour at room temperature, and the

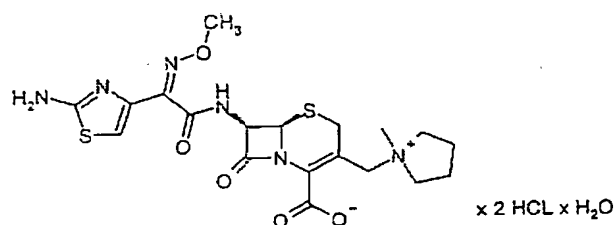
product is subsequently isolated through a suction filter. The product is washed with a total of 500 ml of acetone and dried for ca. 18 hours at room temperature in a vacuum drying chamber.

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Yield	45.01 g
purity HPLC:	99.7 area percent

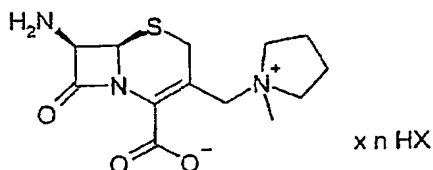
Claims

1. A process for producing the compound of formula I



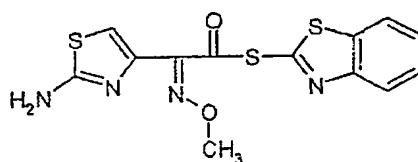
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wherein a compound of formula II



wherein X is chloride or iodide and n is 0 to 2 in
unsolvated or solvated form is reacted optionally after
10 addition of a base with the compound of formula III

III



in acetone or aqueous acetone and the compound of
formula I is isolated from the reaction mixture by
addition of HCl.

15

2. A process as claimed in claim 1, wherein
pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-

azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate is used.

3. A process as claimed in claim 1, wherein
5 pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-aza-
bicyclo[4.2.0]oct-2-en-yl)methyl]-chloride is used,
optionally in solvated form.
4. A process as claimed in claim 1, wherein
10 pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-aza-
bicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride is
used, optionally in solvated form.
5. A process as claimed in any one of claims 1 to 4,
15 wherein a C₁-C₈-trialkylamine, KOH or NaOH, or an alkali
hydrogen carbonate or potassium carbonate, is used as
the base.